Current Biology, Vol. 13, 990–999, June 17, 2003, ©2003 Elsevier Science Ltd. All rights reserved. DOI 10.1016/S0960-9822(03)00377-4

Multimodal Spatial Representations Engaged in Human Parietal Cortex during Both Saccadic and Manual Spatial Orienting

Emiliano Macaluso,[1,*] Jon Driver,[1,2] and Chris D. Frith[2]
[1]Institute of Cognitive Neuroscience
University College London
17 Queen Street
London, WC1N 3AR
United Kingdom
[2]Wellcome Department of Imaging Neuroscience
Institute of Neurology
Functional Imaging Laboratory
12 Queen Street
London, WC1N 3BG
United Kingdom

Summary

Background: Recent neuroimaging studies have found that several areas of the human brain, including parietal regions, can respond multimodally. But given single-cell evidence that responses in primate parietal cortex can be motor-related, some of the human multimodal activations might reflect convergent activation of potentially motor-related areas, rather than multimodal representations of space independent of motor factors. Here we crossed sensory stimulation of different modalities (vision or touch, in left or right hemifield) with spatially directed responses to such stimulation by different effector-systems (saccadic or manual).
Results: The fMRI results revealed representations of contralateral space in both the posterior part of the superior parietal gyrus and the anterior intraparietal sulcus that activated independently of both sensory modality *and* motor response. Multimodal saccade-related or manual-related activations were found, by contrast, in different regions of parietal cortex.
Conclusions: Whereas some parietal regions have specific motor functions, others are engaged during the execution of movements to the contralateral hemifield irrespective of both input modality and the type of motor effector.

Introduction

In daily life, we often take for granted our ability to perceive external space and to act spatially within it, but this overlooks some complex issues. Space is coded by several different sensory systems (e.g., vision and touch), each of which begins with a different spatial organization (i.e., retinotopic versus somatotopic). Moreover, we can respond with many different effector systems (e.g., eyes or hands), each of which has different spatial constraints. One possible neural architecture for achieving integrated spatial behavior is the construction of multimodal spatial representations that can provide signals in several frames of reference, thus allowing generation of different types of motor behavior [1, 2]. Single-cell studies in animals have revealed that several brain regions contain neurons responding spatially to stimuli from multiple sensory modalities [2–7], typically having spatially aligned receptive fields [5, 8, 9]. These regions include several parietal areas [5, 7, 8] that not only receive afferent inputs from different sensory modalities [10, 11] but also send direct efferent projections to particular premotor and prefrontal areas involved in one or another type of motor response [12–14].

Recently, brain imaging techniques have been used to search for multimodal brain areas in humans [15–19]. In one representative study [18], vision, touch, or audition was stimulated. In comparison with baselines, all three modalities activated ventral intraparietal sulcus and inferior parietal cortex (plus premotor regions), consistent with convergence of different sensory modalities to human parietal cortex. However, spatial location was not manipulated systematically in this or related multimodal studies [16, 17, 19]. Other crossmodal studies used localization tasks [20], but without comparing multimodal brain responses for sensory events at different locations. In the present study, the use of event-related fMRI with varied target locations allowed us to investigate multimodal brain responses that do depend on stimulus location (i.e., multimodal spatial representations).

A more critical interpretative difficulty arises for some previous imaging studies that sought to identify human brain areas responding spatially to stimuli from multiple modalities. Such brain responses could in principle reflect *motor-related* activations (e.g., some nascent intention to move toward the location of the relevant stimulus). This has long been a thorny issue in the monkey single-cell literature on parietal cortex. Many ingenious efforts have been made in single-cell work to separate representations of stimulus location from activity related to a particular motor response orientation toward that location. Several recent studies [2, 21, 22] suggested that cellular activity in some regions of posterior parietal cortex (in and around the intraparietal sulcus) can reflect a monkey's intention to perform a particular type of motor response (e.g., with eye versus hand [21]; but see also [23]) toward a location within the cell's receptive field, whereas other studies have suggested that the critical factor can sometimes be the task-relevance of a particular location, regardless of the motor response that will be made to it [24–26].

Here we used fMRI to examine multimodal spatial representations in human parietal cortex and, critically, to determine whether activations in any such regions depend on the type of spatial motor response required. We stimulated different sensory modalities (vision or touch) in the left or right hemifield during two motor tasks: saccadic eye movements or manual button presses. The modality of the target and the type of spatial motor response changed only between predictable epochs, whereas the side of the target was unpredictable for each trial. Subjects made a lateralized response

*Correspondence: e.macaluso@fil.ion.ucl.ac.uk

(either a saccade or a button press) to the side of the target. Using visual or tactile stimuli at different locations (left or right) allowed us to highlight any brain activations that depended on target position (e.g., contralateral activations), and also to assess whether these were restricted to stimulation of just one particular modality (vision or touch) or instead applied for both (thus indicating multimodal spatial specificity). Critically, crossing these manipulations with the use of two different motor tasks further allowed us to address the central question of whether different parietal regions are involved in representing spatial locations multimodally when different effector systems are used to execute a spatially directed motor response toward the target location. Alternatively, some areas might represent behaviorally relevant locations irrespective not only of the stimulated modality (vision or touch) but also of the type of spatial motor response (with eye or hand).

Results

We measured overt responses throughout each scanning session by using an eye-tracking system with remote optics, plus electronic switches on each side to record manual button presses. Saccadic latencies were defined by horizontal eye position exceeding 2° of visual angle from central fixation. Analysis of behavioral data revealed only a main effect of the type of movement ($p < 0.001$), with saccades yielding faster reaction times (means of 366 ms for saccades and 503 ms for button presses; but note that the exact size of this effect will depend on the eye movement parameter—here, horizontal eye position—used for determining saccadic reaction times). Figure 1 shows horizontal eye position separately for each subject in each condition, with these traces time-locked to saccade onset (see also Experimental Procedures). Note that no systematic eye movements toward the target side in particular occurred during analyzed trials requiring manual responses (blue and cyan traces in Figure 1).

Analysis of the imaging data was aimed at isolating brain areas involved in three main processes: (1) performance of different types of spatial motor response (movement-related activations for saccades or manual responses); (2) multimodal activations dependent on target side, but independent of both target modality *and* type of response; and (3) any possible interactions between modality of the target and type of overt response.

As expected, manual responses activated the superior precentral gyrus contralateral to the response side (see Table 1; also Figure 2, green and red). In addition, increased activity for responses with the contralateral hand were also detected in the anterior part of the superior parietal gyrus (see Table 1), confirming the presence of hand-related functions in human parietal cortex. The saccade task activated a more caudal region in posterior intraparietal sulcus (pIPS) than was found for hand-movements. Unlike the hand-related effects, the parietal activations for saccades were found bilaterally and irrespective of response side (see signal plots 2E and 2F). The saccade task also bilaterally activated a region at the junction of superior frontal sulcus with precentral sulcus, possibly in correspondence with the human homolog of the frontal eye field (FEF, see Figures 2A and 2B) [27]. Additionally, medial occipital cortex also showed increased activity during saccades. The portion of this medial occipital activation lying in the calcarine fissure showed a significant effect of saccade direction, with higher activity for saccades toward the ipsilateral side (see Table 1). These occipital activations are likely to reflect the changes in visual input when the eyes moved (which would apply equally after visual and tactile targets in our procedure; see Experimental Procedures). This is unlikely to be the case for frontal and parietal effects, for which single-cell recordings have found neurons that respond not only during saccade execution (which will typically produce some change in the retinal input), but also during saccade preparation [26, 28]. Overall, these initial results highlight two sepa-

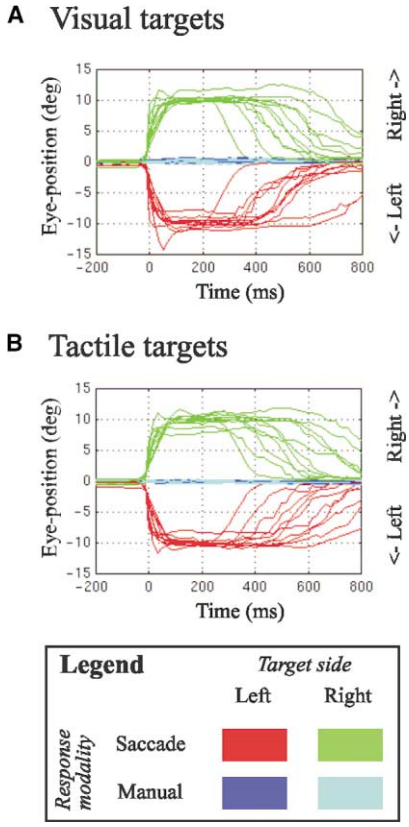

Figure 1. Eye Position for the Eight Trial Types

Horizontal eye position traces for each subject are plotted according to the modality of the target ([A] visual; [B] tactile), the target side (left or right), and the type of motor response (manual or saccades). Eye position traces are time-locked to the saccade onset for saccade trials and to the time of the button press for the manual trials. For each subject, as expected, this shows a sharp change in eye position during the saccade trials (red and green traces), but no systematic change for trials requiring manual responses (blue and cyan, data overlap in figure), once trials containing detected losses of fixation are removed (see Experimental Procedures). For the saccade trials, saccade amplitudes were calculated as the mean eye position in a 100 ms window, starting 100 ms after saccade onset (i.e., not including the initial eye position shift). For visual trials, this gave a mean amplitude of 9.97 degrees; for tactile targets, this was 9.76 degrees.

Table 1. Effects Related to the Type of Overt Response, Manual or Saccadic, and Dependence of These upon Movement Side.

Manual	Anatomical Area	Coordinates	Z-value	p-corr.
Left hand	R-precentral gyrus	46, −18, 62	>8	<0.001
	L-cerebellum	−20, −50, −26	6.3	<0.001
	R-insula	38, −20, 12	5.8	<0.001
	R-cingulate gyrus	8, −4, 50	5.8	<0.001
	R-anterior SPG	36, −40, 66	4.8	0.021
Right hand	L-precentral gyrus	−38, −24, 66	>8	<0.001
	R-cerebellum	18, −54, −22	7.3	<0.001
	L-anterior SPG	−32, −44, 62	5.8	<0.001
Saccades				
Both sides	L-posterior IPS	−20, −66, 58	>8	<0.001
	R-posterior IPS	26, −60, 58	7.5	<0.001
	L-frontal eye-field	−52, −2, 48	7.0	<0.001
	R-frontal eye-field[a]	50, −2, 48	7.2	<0.001
	L-medial occipital cortex	−6, −80, −6	>8	<0.001
	R-medial occipital cortex	10, −68, 0	>8	<0.001
Leftward	L-calcarine	−12, −82, 10	5.6	0.001
Rightward	R-calcarine	16, −80, 6	5.1	0.007

Corrected p-values were assigned with the whole brain considered to be the search volume.
[a] Only the activation of the right frontal eye field for saccadic responses did not pass the minimum cluster size threshold of 25 voxels. (SPG: superior parietal gyrus; IPS: intraparietal sulcus; R/L: right/left hemisphere)

rate networks involved in eye versus hand movements, both of which included different sub-regions of superior parietal cortex. These results also show for the first time that both circuits can be activated when either visual or somatosensory input is used (see colored bars in Figures 2A–2F) to direct spatial motor responses.

We next investigated the most critical issue—whether there exist any spatial representations that are engaged irrespective of both sensory modality *and* type of motor response. We directly compared trials involving one hemifield versus the other, now irrespective of both the modality of sensory stimulation and also the type of overt response. This analysis revealed increased activity in the posterior part of the superior parietal gyrus (pSPG) and also in the anterior part of the intraparietal sulcus (aIPS); see Figure 3 and Table 2. These spatially specific activations were always found to be contralateral to the side of the target but were otherwise symmetrically between hemispheres (see activations in green and red in Figure 3; note also that only the result for left aIPS did not reach full corrected significance, see Table 2). Signal plots confirm that in both pSPG and aIPS there was greater activity for contralateral targets compared with ipsilateral targets (see Figures 3A–3D; note that the critical spatially specific effects are the pairwise difference between those bars that are linked in these graphs by yellow lines; see also the Figure 3 legend). Critically, this differential activity as a function of target side was observed irrespective not only of target modality but also of motor response type, thus revealing *multimodal* but *effector-independent* spatial activations for these particular parietal regions. For comparison, the anatomical sections in Figure 3 also show the location of the posterior intraparietal activation observed for saccadic responses (pIPS, blue; see also Figure 2). This region was posterior to the areas showing multimodal contralateral spatial activations independent of effector (i.e., pSPG and aIPS), thus revealing functional *segregation* of saccade-related circuitry versus multimodal spatial representations in human parietal cortex (see also the bottom of Figure 3 for a transverse section).

Finally, the use here of two target modalities (vision and touch) and two response types (saccades and manual button presses), in a fully factorial design, allowed us to test for any brain activations related to specific sensory-motor combinations. Interactions between target modality and response type were found in the inferior/lateral part of the intraparietal sulcus (iIPS); see Figure 4 (magenta). This region was anatomically distinct from both the saccade-related region in posterior intraparietal cortex (i.e., pIPS: Figures 2 and 3, blue) and the two parietal areas showing multimodal contralateral spatial activations independently of the responding effector (i.e., pSPG and aIPS, Figure 3, green and red). Peak activations were detected at x, y, z = 50, −46, 56 (Z = 4.3; p-corr. = 0.022) in the right hemisphere and x, y, z = −40, −50, 56 (Z = 3.9; p-corr. = 0.089) in the left hemisphere. Figure 4 shows anatomical details for this inferior intraparietal region (labeled as iIPS: magenta), plus the pattern of activity in this region for all eight conditions. As a functional reference, the anatomical sections in Figure 4 also display the location of regions showing multimodal contralateral spatial activations (only pSPG is visible in these sections: green and red). Signal plots (Figures 4A and 4B) indicate that the inferior intraparietal area (iIPS; magenta) was not selectively activated for only one specific combination of sensory-motor transformation but rather that it was involved both for manual responses to visual targets and also for saccades to tactile targets (see magenta bars in Figures 4A and 4B). Both of these sensory-motor combinations may require more complex coordinate transformations (retinocentric to hand-related, and somatotopic to oculomotor) than the direct sensory-motor mapping required during either saccades to visual targets or manual responses to tactile targets on the corresponding hand.

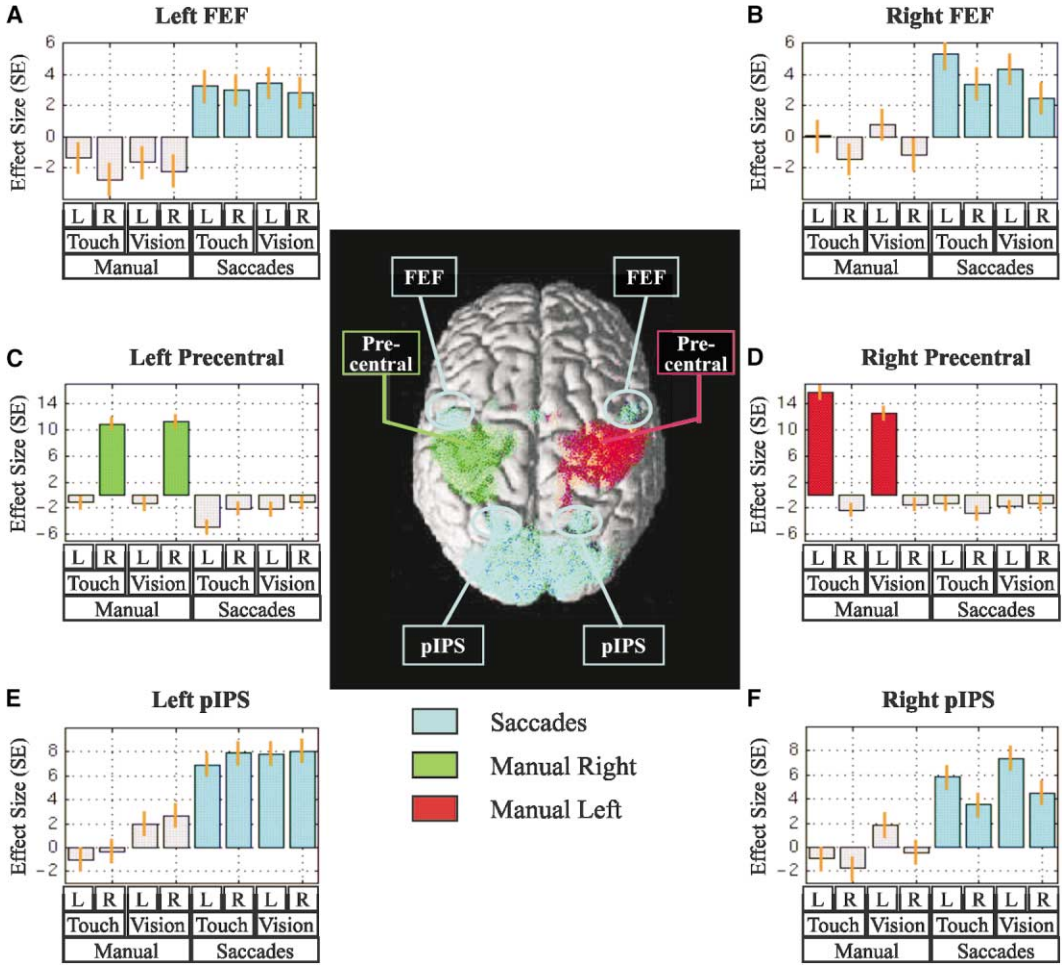

Figure 2. Movement-Related Imaging Results

Movement-related activations are rendered on the surface of the canonical MNI brain template (top view). Brain activations for manual trials were lateralized to the contralateral hemisphere and are displayed according to the responding hand (right hand in green; see also panel [C]; left hand in red, panel [D]). Note that in addition to precentral cortex, contralateral hand effects extended also to the anterior part of the superior parietal gyrus (see also Table 1). Brain activations for saccades (in blue) were largely independent of target side and were found bilaterally in the left and right hemispheres. Signal plots show activation for all eight experimental conditions. Plots refer to activity at the maxima (see Tables for corresponding coordinates), and effect sizes are expressed in standard error (SE) units, as for Figures 3 and 4 also. The colored bars highlight effects relevant for movement-related activities or any laterality of them. For all SPM thresholds, p-uncorr. = 0.001; L/R, left right; pIPS, posterior intraparietal sulcus; and FEF, frontal eye-field.

Discussion

The present study manipulated side (left or right) and modality (visual or tactile) of a target stimulus, plus the type of spatially directed motor response that the target stimulus required (saccade or manual button press). The use of targets at different positions and in different modalities allowed us to identify brain areas showing responses that were spatially specific for stimulation of one or the other hemifield but that were independent of the modality of stimulation (i.e., spatial representations that are "multimodal" in this sense). Critically, our further crossing of these manipulations with the use of two different motor tasks assessed whether the engagement of such multimodal spatial representations depends on the type of movement required. The results demonstrated the existence of multimodal spatial representations in contralateral regions of human parietal cortex and critically showed for the first time that these can be activated multimodally irrespective of the spatial motor task (eye or hand). These results thus indicate that specific regions of parietal cortex may code behaviorally relevant spatial locations in a manner that depends neither on the modality of stimulation nor on the final motor command required to execute the motor task.

Two parietal regions showed such multimodal spatial activations. These were the posterior part of the superior parietal gyrus (pSPG) plus the anterior part of the intraparietal sulcus (aIPS), in both of which activity was higher for contralateral than for ipsilateral targets regardless of not only stimulus modality but also the type of motor response. Activity in the intraparietal sulcus has been previously reported in several studies that used visual and tactile stimulation (e.g., [18]). Elsewhere we have demonstrated contralateral spatial selectivity in anterior intraparietal cortex during tasks of endogenous

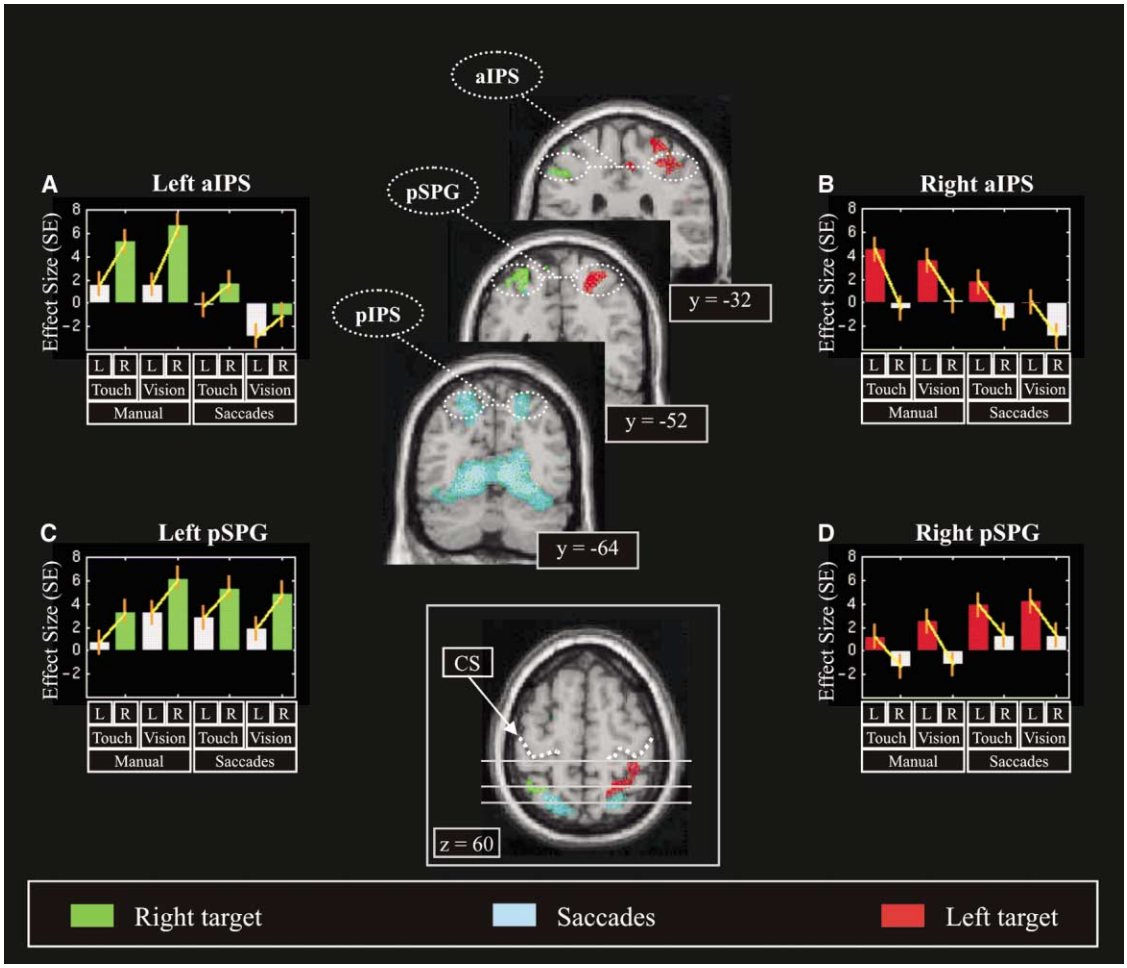

Figure 3. Multimodal Spatial Activations

Anatomical location and signal plots for the regions showing higher activity for contralateral than for ipsilateral targets, regardless of stimulus modality and response type. Pairwise comparisons (between the conditions linked with yellow lines in the graphs) of activity for right minus left targets demonstrates higher activity for contralateral right targets (A and C) in two regions of the left hemisphere (pSPG and aIPS); activations on the coronal shown in green. Conversely, in the corresponding right-hemisphere regions, activity was consistently higher for left targets than for right targets (red [B and D]). Critically, these contralateral spatial activations were observed regardless not only of the modality of the target (vision or touch) but also of the type of overt response (manual or saccade); see signal plots. Note that relative differences between paired conditions (see yellow connecting lines in graphs) are more informative than absolute values in these plots, given that responses were not measured against rest. The plotted effects represent changes from ongoing activity when subjects knew that either a left or a right target could be presented and prepared for a prespecified movement type (i.e., saccade or key press). The anatomical sections also display the location of the more posterior intraparietal activation observed bilaterally for saccadic responses (blue; see also Figure 2), highlighting the anterior/posterior segregation of contralateral multimodal spatial activations (red/green) versus saccadic activity (blue) along the intraparietal sulcus. For all SPM thresholds, p-uncorr. = 0.001; L/R, left right; pSPG, posterior superior parietal gyrus; aIPS, anterior intraparietal sulcus; pIPS, posterior intraparietal sulcus; and CS, central sulcus.

Table 2. Multimodal Spatial Effects as Revealed by Conjunction Analysis

Multimodal Spatial Effects	Anatomical Area	Coordinates	Z-value	p-corr.
Left targets	R-anterior IPS	38, −36, 54	5.0	0.002
	R-posterior SPG	24, −54, 60	4.6	0.007
	R-posterior SPG	24, −34, 68	4.6	0.007
Right targets	L-anterior IPS	−48, −32, 46	3.7	0.202
	L-posterior SPG	−34, −56, 64	4.6	0.010

Activations for targets in the contralateral hemifield were detected in the posterior part of the superior parietal gyrus (pSPG) and anterior intraparietal sulcus (aIPS), for both hemispheres. Corrected p-values were assigned with the whole of the parietal lobe contralateral to the target side considered to be the search volume. The left aIPS result, which did not survive correction, is reported here for completeness (SPG: superior parietal gyrus; IPS: intraparietal sulcus; R/L: right/left hemisphere)

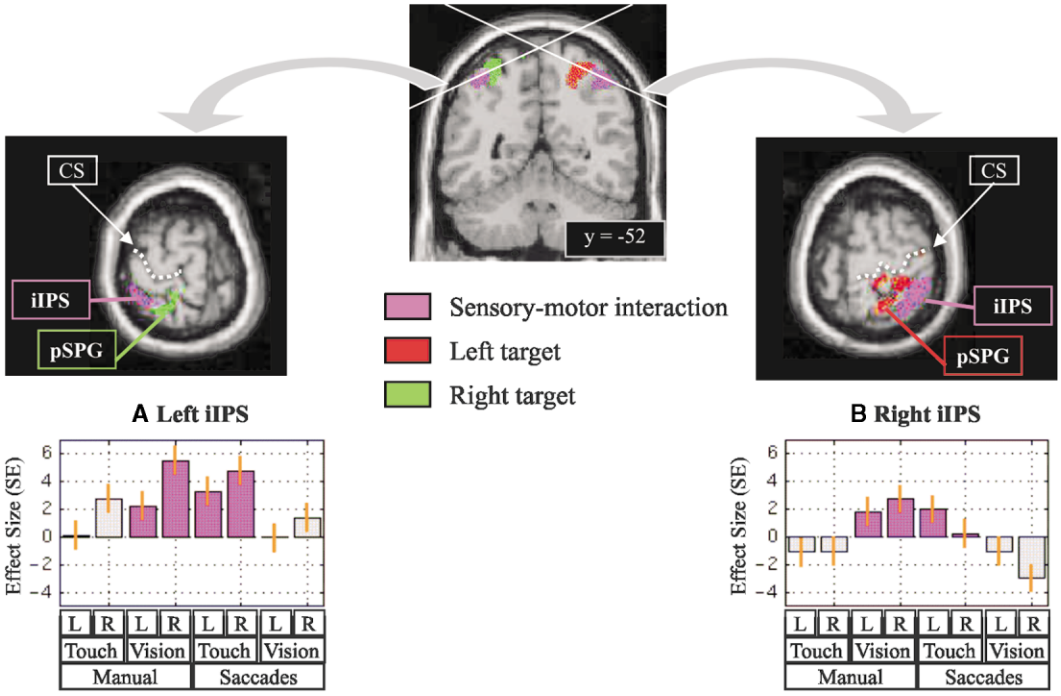

Figure 4. Sensory-Motor Interactions

Location and signal plots for the parietal regions that activated during both manual responses to visual targets and saccades to tactile targets (in magenta, see also signal plots [A and B]). The anatomical sections (with the coronal section in the center indicating the position of the two tilted (23 degrees) transverse sections) also display the location of the areas showing multimodal spatial effects (red and green; see also Figure 3), again highlighting functional segregation within human parietal cortex. For all SPM thresholds, p-uncorr. = 0.001; L/R, left right; SPG, superior parietal gyrus; iIPS, inferior intraparietal sulcus; and CS, central sulcus.

spatial attention, when subjects attended covertly to one or the other hemifield for either vision or touch during bilateral stimulation [29, 30] rather than during unilateral stimulation with overt motor responses, as done here. In this previous work, activity increased for attention to the contralateral hemifield, irrespective of stimulated [29] or attended [30] modality (see also [31] for related findings during passive stimulation in vision or touch). The present findings go beyond all these results by showing that even in the context of *overt* spatial orienting of different types (here saccades or lateralized manual responses), activity in parts of the superior parietal gyrus and anterior intraparietal sulcus is affected by target location but not by target modality and, critically, not by motor-response type, either. This suggests that the current motor set is not critical for activating these multimodal spatial representations in parietal cortex.

We should note that the present design did not separate the *intention* to move toward one or the other hemifield from the actual *execution* of the overt spatial movement. Thus, a possible interpretation for the common contralateral activation in some regions of parietal cortex for both saccadic and manual responses is that these areas are associated with an early stage of movement planning (rather than movement execution) when the final type of motor command is still not specified. This might accord with the notion that parietal cortex contains some spatial representations that emphasize the current relevance of a given location, irrespective of the particular motor task [24, 26] (but see also [23]). Another issue concerns the possibility that, irrespective of the current instruction and intention to respond with either an eye-movement or a button-press, the sudden onset of a peripheral stimulus might automatically engage initial stages of planning for both movement types. This difficult issue has long been debated within the single-cell literature on parietal cortex (e.g., see [26, 28]). Although our study alone is unlikely to end this debate, our finding of both motor-specific (see below) *and* motor-independent activation in parietal cortex does indicate some segregation between areas specifically involved in one type of motor task only and those engaged irrespective of the final motor command. Future experiments could use multisensory imaging paradigms similar to the one introduced here to separate brain activity associated with the planning versus execution of different types of movements by introducing variable delays between target and movement execution. Such studies may reveal whether the multimodal and motor-independent activations reported here relate to just a preparatory phase or can be observed during movement execution itself. In any case, the present results already indicate that at some stage in sensory-motor transformation, selection of relevant locations activates the posterior part of the superior parietal gyrus (pSPG) and the anterior part of the intraparietal sulcus (aIPS) contralaterally, irrespective of the type of movement to be performed toward that location or the sensory modality of the target there.

Different patterns of activation were detected in other regions of parietal cortex. In two distinct parietal regions, activity increased either for conditions requiring saccadic responses (pIPS, see Table 1; plus figures 2 and 3, blue) or for those requiring responses with the contralateral hand (aSPG: see Table 1). The finding of specific eye-related versus hand-related motor functions in parietal cortex is consistent with electrophysiological data in non-human primates [21], as well as with previous imaging [32–33] and patient studies [34] in humans. Moreover, the posterior/anterior (corresponding to eye/hand) layout of these motor-specific activations fits with other recent imaging studies that employed spatially directed movements with the eyes or the hand [33, 35]. The present fMRI study indicates for the first time in humans that these motor-related parietal areas can be activated when sensory input from entirely different modalities (here vision or touch) is used to direct either saccadic eye movements, or lateralized manual responses. Thus, in addition to our central finding of contralateral multimodal spatial representations that appear to be independent of specific motor requirements (in pSPG and aIPS), we also found multimodal effects in pIPS and aSPG that displayed effector-specific activations for eye or hand movements, respectively.

Unlike previous electrophysiological studies on sensory-motor interactions [36], which traditionally employed primarily visual or occasionally auditory stimuli, the present study included lateralized tactile stimuli as targets, with all movements made in peripersonal space. This may account for the localization of the critical multimodal spatial effects in anterior and dorsal parietal cortex. Note that although these anterior and dorsal parietal regions are often considered part of a parietal (and ventral premotor) network selectively involved in reaching and grasping but not saccades (e.g., [12, 14, 37]), some other new evidence suggests that such effector-specific segregation might be less rigid than initially thought in some areas. For instance, some saccadic activity has been recently reported in putative parietal "reach" regions [23], and saccade-related responses in subregions of ventral premotor cortex [38] have also been reported.

The localization of motor-independent contralateral multimodal effects in anterior/dorsal parietal cortex in the present study accords with other imaging studies manipulating tactile (and visual) spatial attention [29, 30], specifically in situations in which attention was focused in peripersonal space near to the hands. It also accords with the prominent tactile input to these regions. In monkeys, anterior/dorsal regions of parietal cortex (area 5 and the anterior intraparietal area AIP) receive afferent projections from several somatosensory areas [10, 11] and are thought to be involved in visual-tactile integration for spatial behavior in proximal space [14, 39, 40]. The more posterior/superior contralateral, multimodal, and motor-independent activations that we report (in pSPG, see Figures 3C and 3D) extended from superior parietal gyrus to the upper bank of the intraparietal sulcus and might include portions of area MIP. In monkeys, MIP contains multimodal visuo-tactile neurons [41] and, together with area 5 and area AIP, again appears to be involved in action within peripersonal space [26, 42], as shown here.

Our study also found activation of different (more inferior) intraparietal regions for both key presses in response to visual targets and saccades in response to tactile targets. This inferior activation included the lateral/ventral bank of the intraparietal sulcus and extended to the superior part of the supramarginal gyrus. A possible interpretation for this effect is that key presses in response to visual targets and saccades in response to tactile targets may involve additional transformations of reference frames (retinocentric to hand-related, and somatotopic to oculomotor) that are not required for more direct stimulus-response mapping, as in saccades in response to visual targets or manual responses to tactile targets on the corresponding hand. This interpretation would fit with the postulated role of some parietal regions in sensory-motor transformations [2, 43].

Conclusions

The present study identified contralateral multimodal spatial representations that activated in human parietal cortex not only in response to different types of sensory stimulation but also independently of the nature of the spatial motor response to that stimulation. We found that the posterior part of the superior parietal gyrus and the anterior part of the intraparietal sulcus showed higher activity for contralateral versus ipsilateral targets. Critically, this spatial specificity was observed irrespective not only of the sensory modality of the target (vision or touch) but also of the type of overt motor response that was executed (saccadic or manual button presses). This highlights the role of task-relevant stimulus location in these parietal regions, rather than the current motor task. By contrast, other regions of parietal cortex were selectively activated either for saccadic eye movements or for manual responses. The present results thus indicate some dissociation between multimodal spatial coding and processes associated with executed motor response within human parietal cortex, and they support the existence of intermediate spatial representations that are engaged irrespective of stimulus modality and response type.

Experimental Procedures

Subjects

Eleven volunteers participated. All were right-handed males, with a mean age of 28 years (range 22–36). After receiving an explanation of the procedures, subjects gave written informed consent. The study was approved by the Joint Ethics Committee of the Institute of Neurology and the National Hospital for Neurology and Neurosurgery.

Paradigm

Functional MRI data were acquired via a mixed blocked/event-related protocol. Eight event types were organized in a $2 \times 2 \times 2$ factorial design. One factor was the modality of the peripheral target (visual or tactile; blocked). The second factor was the type of spatially directed overt motor response (saccades or manual button presses to the side of the target; also blocked). The third factor was the side of the target (left or right hemifield; unpredictable on each trial).

The modality of the target and the type of motor response were blocked in order to minimize any task-switching requirements. Each block lasted approximately 19 s, during which a total of four targets were presented unpredictably in either the left or right hemifield,

and four responses to the appropriate location were made. The color of a central fixation point specified the type of response that was required throughout each block (i.e., saccades or manual responses). Each subject underwent four separate scanning sessions, lasting approx. 5.5 min each.

Stimuli and Task

Subjects lay in the scanner and rested each hand on a plastic support on the corresponding side. On each side there was an LED cluster for presenting visual stimuli and a piezoelectric component (T220-H3BS-304, Piezo Systems Inc., Cambridge, USA) for delivering unseen tactile stimulation to the thumb. The peripheral LEDs and the subject's thumbs were 10° of visual angle from a central LED. The peripheral LEDs were placed directly in front of the thumbs, so that visual and tactile stimuli could be delivered in close spatial proximity on either side (see also [44] for a schematic illustration of the apparatus; but note that here tactile stimuli were delivered via piezoelectric components rather than air-puffs and that the two LEDs within each side were now a directly adjacent pair). The scanner environment was dimly lit, and subjects viewed all LEDs and both hands through a mirror system. This comprised two mirrors placed on top of the whole-head RF coil, such that LEDs and the subject's thumbs could be viewed without any mirror-image reversal. Placement of a third mirror on top of the RF coil allowed monitoring of eye-position with a remote optics eye-tracker throughout the experiment (see below).

The central LED was illuminated throughout the scanning session, with its color (green or yellow) indicating the type of movement (i.e., saccades or manual responses) that was required throughout the current block. The association between LED color and type of responses was arbitrary and counterbalanced across subjects. During each trial, a target stimulus was presented for 50 ms in either the left or right hemifield. According to the color of the central LED, the subject either performed a saccade to the target side (saccade conditions) or pressed a button with the unseen index finger on the side of the target (the subject used the left or the right hand, depending on the target side). The tasks were performed irrespective of the modality of the target (visual or tactile). Note that because of the short time of target presentation (50 ms), the type of overt response should not affect the experimental sensory input (i.e., visual targets were extinguished before saccade initiation), excluding any trivial sensory-motor interactions.

The modality of the target and the type of motor responses were blocked in 19 s epochs. Within each block there were four target/response trials (equiprobable for left and right hemifields). The mean intertrial interval was 4.61 s (range: 2.32–13.03 s), with the occurrence of the target fully unpredictable. During each session, there were 64 target/response events (16 for each sensory-motor combination: saccade to visual target, saccade to tactile target, button-press to visual target and button-press to tactile target).

Image Acquisition

Functional images were acquired with a 2 Tesla Magnetom VISION MRI scanner (Siemens, Erlangen, Germany). BOLD (blood oxygenation level-dependent) contrast was obtained via echo-planar T2* weighted imaging (EPI). The acquisition of 32 transverse slices gave coverage of the whole cerebral cortex. Repetition time was 2.43 s. The in-plane resolution was 3×3 mm.

Data Analysis

Data were analyzed with SPM99 (www.fil.ion.ucl.ac.uk). For each subject, we corrected acquisition timing by using the middle slice as a reference [45], and the 524 volumes were realigned with the first volume. To allow intersubject analysis, we normalized images to the Montreal Neurological Institute (MNI) standard space [46] by using the mean of the 524 functional images. All images were smoothed with a 10 mm isotropic Gaussian kernel.

Statistical inference was based on a random-effects approach [47]. This comprised two steps. First, for each subject, the data were best-fitted (least square) at every voxel via a linear combination of effects of interest, plus confounds. The effects of interest were the timing of the eight target/response event types (given by crossing of the three factors: target modality, response type, and side). In addition, the transitions between different blocked motor responses (saccadic or manual, as signaled by changes of the color of the central fixation point) were modeled as effects of no interest. All event types were convolved with the SPM99 standard hemodynamic response function. Trials containing losses of fixation (see below) were modeled as confounds. Linear compounds (contrasts) were then used for determining the effect for each of the eight target/response conditions across the four sessions, producing one image per condition per subject. These contrast images then underwent the second step, which comprised a multiple regression that modeled condition and subject effects. Again, linear compounds were used for comparing the eight target/response conditions, but now between-subjects variance (rather than variance between scans) was used.

Our analyses aimed to identify brain regions involved in three types of processes: motor performance, multimodal spatial representations, and any interactions between target modality and response type. Movement-related activities were further separated into side-specific versus side-independent categories. We investigated side-specific activations by using the effect of side for one type of movement (e.g., left versus right button presses), at a threshold of p-corr. $= 0.05$, corrected for multiple comparisons. To ensure that any such effect of side was indeed specific to one type of movement, we adopted the additional constraint that all voxels showing any effect of side should also show an interaction between side and type of movement (p-uncorr. $= 0.01$). Note that any such additional constraint can only make our analysis more conservative. We assessed side-independent movement activations by using conjunction analysis [48]. This tested for brain regions activated for one type of movement versus the other, irrespective of the direction of the movement and the modality of the target (i.e., conjunction of the four simple effects of movement-type; conjunction p-value $<$ 0.05, corrected for multiple comparisons).

We also detected multimodal spatial effects by conjunction analysis [48, 49], by using the simple effect of side (left versus right, or vice-versa) for the four types of target-response combination (saccade to vision, saccade to touch, button press to vision, and button press to touch). This analysis tested for spatially specific brain activations common to all types of target-response combination (i.e., activations dependent on target side but independent of both the modality of the target and the type of overt response). Note that because the fMRI signal relies on the activation of large populations of neurons, this analysis cannot directly show that common activation occurred at the level of each single cell in an activated voxel or cluster. In principle at least, intermixed neurons with different specificity for one or another modality and/or movement type could give rise to an apparently unspecific activation in the fMRI analyses. However, existing electrophysiological knowledge concerning response properties of single neurons in any activated area can aid the interpretation of fMRI data, and the parietal areas activated here are known to contain multimodal neurons based on animal studies [39, 41]. Finally, the factorial nature of our imaging design also allowed us to test directly for any interactions between modality of the target and type of motor response.

Given previous evidence on the role of parietal cortex in multimodal spatial representation and sensory-motor interactions [26, 28], for the latter two comparisons (i.e., multimodal spatial effects, plus any interactions) we used a volume of interest comprising the whole parietal lobule to assign corrected p-values. Because we expected any spatially specific multimodal effects in parietal cortex to be contralateral to the side of the stimulation [29, 31], for this comparison only we used the contralateral parietal lobule for the correction [50] (but note that relaxing this constraint did not reveal any activation of parietal cortex ipsilateral to the target side). For completeness, we also report any contralateral effects in parietal cortex that reached $p < .001$ uncorrected when these fell in symmetric regions to a corrected activation for effects contralateral to the presented target in the other hemisphere. All other effects are reported as significant only after correction for multiple comparison with the whole brain as the volume of interest, plus a minimum cluster-size threshold of 25 voxels.

Eye Tracking

Eye position was monitored with an ASL Eye-Tracking System that was custom adapted for use in the scanner (Applied Science Labora-

tories, Bedford, MA; Model 504, sampling rate = 60 Hz). Eye position traces were examined in a 1506 ms window, beginning 132 ms prior to the target onset. For trials requiring central fixation (i.e., blocks of manual responses), losses of fixation were identified as changes greater than 2° in horizontal eye position. This revealed that subjects lost fixation in 13% of the trials requiring central fixation. After removal of these trials, no systematic gaze deviation could be found in any of the conditions requiring maintenance of central fixation (i.e., manual-response conditions; see Figure 1, cyan and blue lines, which overlap closely). Lowering the detection threshold to 1° resulted in the expected increase of rejected trials, but inspection of the traces for these additional trials (movements between 1° and 2°) did not reveal any systematic eye movements toward the target location. The 2° threshold thus seems appropriate for excluding trials in which the eyes shifted systematically toward the target position. We modeled these excluded trials separately in the imaging data analysis to ensure that they would not affect our imaging results. Note that in any case, any residual small ($< 2°$) and nonsystematic eye movements during the manual task seem highly unlikely to elicit the same side-specific brain activity as the systematic large movements observed during the saccade trials (compare red and green traces with blue and cyan traces in Figure 1). For trials requiring saccadic responses, reaction times were calculated as the time between target onset and horizontal eye position exceeding the 2° threshold.

In addition, to assess any possible muscular activity for the hand during the saccade task, we measured electromyography (EMG) in three volunteers outside the scanner by using the identical design as in the fMRI experiment. The recordings from the first dorsal interosseus did not show any muscular activity during the saccade task, with the exception of just two occasions over a total of 384 trials. This suggests that the saccadic task does not induce hand movements, even when saccade and manual blocks are interleaved.

Acknowledgments

E.M. and J.D. were supported by a Programme Grant from the Medical Research Council (United Kingdom). C.F. and the Functional Imaging Laboratory at the Wellcome Department of Neuroimaging were supported by the Wellcome Trust. This research was facilitated by the MRC Co-operative for "Analysis of cognitive impairment and imaging of cognition" at University College London. J.D. holds a Royal Society-Wolfson Research Merit Award.

Received: February 10, 2003
Revised: April 1, 2003
Accepted: April 3, 2003
Published: June 17, 2003

References

1. Pouget, A., and Snyder, L.H. (2000). Computational approaches to sensorimotor transformations. Nat. Neurosci. *3*, 1192–1198.
2. Cohen, Y.E., and Andersen, R.A. (2002). A common reference frame for movement plans in the posterior parietal cortex. Nat. Rev. Neurosci. *3*, 553–562.
3. Bruce, C., Desimone, R., and Gross, C.G. (1981). Visual properties of neurons in a polysensory area in superior temporal sulcus of the macaque. J. Neurophysiol. *46*, 369–384.
4. Graziano, M.S., and Gross, C.G. (1993). A bimodal map of space: somatosensory receptive fields in the macaque putamen with corresponding visual receptive fields. Exp. Brain Res. *97*, 96–109.
5. Stein, B.E., and Meredith, M.A. The merging of the senses. Cambridge: MIT Press, 1993.
6. Fogassi, L., Gallese, V., Fadiga, L., Luppino, G., Matelli, M., and Rizzolatti, G. (1996). Coding of peripersonal space in inferior premotor cortex (area F4). J. Neurophysiol. *76*, 141–157.
7. Duhamel, J.R., Colby, C.L., and Goldberg, M.E. (1998). Ventral intraparietal area of the macaque: congruent visual and somatic response properties. J. Neurophysiol. *79*, 126–136.
8. Graziano, M.S., and Gross, C.G. The Representation of Extrapersonal Space: A Possible Role for Bimodal, Visuo-Tactile Neurons. (1995). In: The Cognitive Neurosciences, M.S. Gazzaniga, ed. (Cambridge, MA: MIT press), pp. 1021–1034.
9. Graziano, M.S. (1999). Where is my arm? The relative role of vision and proprioception in the neuronal representation of limb position. Proc. Natl. Acad. Sci. USA *96*, 10418–10421.
10. Jones, E.G., and Powell, T.P. (1970). An anatomical study of converging sensory pathways within the cerebral cortex of the monkey. Brain *93*, 793–820.
11. Lewis, J.W., and Van Essen, D.C. (2000). Corticocortical connections of visual, sensorimotor, and multimodal processing areas in the parietal lobe of the macaque monkey. J. Comp. Neurol. *428*, 112–137.
12. Goldman-Rakic, P.S. (1988). Topography of cognition: parallel distributed networks in primate association cortex. Ann. Rev. Neurosci. *11*, 137–156.
13. Petrides, M., and Pandya, D.N. (1984). Projections to the frontal cortex from the posterior parietal region in the rhesus monkey. J. Comp. Neurol. *228*, 105–116.
14. Luppino, G., Murata, A., Govoni, P., and Matelli, M. (1999). Largely segregated parietofrontal connections linking rostral intraparietal cortex (areas AIP and VIP) and the ventral premotor cortex (areas F5 and F4). Exp. Brain Res. *128*, 181–187.
15. Roland, P.E. (1982). Cortical regulation of selective attention in man. A regional cerebral blood flow study. J. Neurophysiol. *48*, 1059–1078.
16. Calvert, G.A., Campbell, R., and Brammer, M.J. (2000). Evidence from functional magnetic resonance imaging of crossmodal binding in the human heteromodal cortex. Curr. Biol. *10*, 649–657.
17. Downar, J., Crawley, A.P., Mikulis, D.J., and Davis, K.D. (2000). A multimodal cortical network for the detection of changes in the sensory environment. Nat. Neurosci. *3*, 277–283.
18. Bremmer, F., Schlack, A., Shah, N.J., Zafiris, O., Kubischik, M., Hoffmann, K., Zilles, K., and Fink, G.R. (2001). Polymodal motion processing in posterior parietal and premotor cortex: a human fMRI study strongly implies equivalencies between humans and monkeys. Neuron *29*, 287–296.
19. Laurienti, P.J., Burdette, J.H., Wallace, M.T., Yen, Y.F., Field, A.S., and Stein, B.E. (2002). Deactivation of sensory-specific cortex by cross-modal stimuli. J. Cogn. Neurosci. *14*, 420–429.
20. Bushara, K.O., Weeks, R.A., Ishii, K., Catalan, M.J., Tian, B., Rauschecker, J.P., and Hallett, M. (1999). Modality-specific frontal and parietal areas for auditory and visual spatial localization in humans. Nat. Neurosci. *2*, 759–766.
21. Snyder, L.H., Batista, A.P., and Andersen, R.A. (1997). Coding of intention in the posterior parietal cortex. Nature *386*, 167–170.
22. Snyder, L.H., Batista, A.P., and Andersen, R.A. (2000). Intention-related activity in the posterior parietal cortex: a review. Vision Res. *40*, 1433–1441.
23. Calton, J.L., Dickinson, A.R., and Snyder, L.H. (2002). Non-spatial, motor-specific activation in posterior parietal cortex. Nat. Neurosci. *5*, 580–588.
24. Wurtz, R.H., Goldberg, M.E., and Robinson, D.L. (1982). Brain mechanisms of visual attention. Sci. Am. *246*, 124–135.
25. Gottlieb, J.P., Kusunoki, M., and Goldberg, M.E. (1998). The representation of visual salience in monkey parietal cortex. Nature *391*, 481–484.
26. Colby, C.L., and Goldberg, M.E. (1999). Space and attention in parietal cortex. Annu. Rev. Neurosci. *22*, 319–349.
27. Petit, L., Clark, V.P., Ingeholm, J., and Haxby, J.V. (1997). Dissociation of saccade-related and pursuit-related activation in human frontal eye fields as revealed by fMRI. J. Neurophysiol. *77*, 3386–3390.
28. Andersen, R.A., Snyder, L.H., Bradley, D.C., and Xing, J. (1997). Multimodal representation of space in the posterior parietal cortex and its use in planning movements. Annu. Rev. Neurosci. *20*, 303–330.
29. Macaluso, E., Frith, C., and Driver, J. (2000). Selective spatial attention in vision and touch: unimodal and multimodal mechanisms revealed by PET. J. Neurophysiol. *83*, 3062–3075.
30. Macaluso, E., Frith, C.D., and Driver, J. (2002). Directing attention to locations and to sensory modalities: multiple levels of selective processing revealed with PET. Cereb. Cortex *12*, 357–368.

31. Macaluso, E., and Driver, J. (2001). Spatial attention and cross-modal interactions between vision and touch. Neuropsychol. *39*, 1304–1316.
32. Kawashima, R., Naitoh, E., Matsumura, M., Itoh, H., Ono, S., Satoh, K., Gotoh, R., Koyama, M., Inoue, K., Yoshioka, S., et al. (1996). Topographic representation in human intraparietal sulcus of reaching and saccade. Neuroreport *7*, 1253–1256.
33. Simon, O., Mangin, J.F., Cohen, L., Le Bihan, D., and Dehaene, S. (2002). Topographical layout of hand, eye, calculation, and language-related areas in the human parietal lobe. Neuron *33*, 475–487.
34. Ro, T., Rorden, C., Driver, J., and Rafal, R. (2001). Ipsilesional biases in saccades but not perception after lesions of the human inferior parietal lobule. J. Cogn. Neurosci. *13*, 920–929.
35. Desouza, J.F., Dukelow, S.P., Gati, J.S., Menon, R.S., Andersen, R.A., and Vilis, T. (2000). Eye position signal modulates a human parietal pointing region during memory-guided movements. J. Neurosci. *20*, 5835–5840.
36. Cohen, Y.E., and Andersen, R.A. (2000). Reaches to sounds encoded in an eye-centered reference frame. Neuron *27*, 647–652.
37. Andersen, R.A., Asanuma, C., Essick, G., and Siegel, R.M. (1990). Corticocortical connections of anatomically and physiologically defined subdivisions within the inferior parietal lobule. J. Comp. Neurol. *296*, 65–113.
38. Fujii, N., Mushiake, H., and Tanji, J. (1998). An oculomotor representation area within the ventral premotor cortex. Proc. Natl. Acad. Sci. USA *95*, 12034–12037.
39. Kalaska, J.F., Scott, S.H., Cisek, P., and Sergio, L.E. (1997). Cortical control of reaching movements. Curr. Opin. Neurobiol. *7*, 849–859.
40. Rushworth, M.F., Nixon, P.D., and Passingham, R.E. (1997). Parietal cortex and movement. II. Spatial representation. Exp. Brain Res. *117*, 311–323.
41. Colby, C.L., and Duhamel, J.R. (1991). Heterogeneity of extrastriate visual areas and multiple parietal areas in the macaque monkey. Neuropsychol. *29*, 517–537.
42. Rushworth, M.F., Nixon, P.D., and Passingham, R.E. (1997). Parietal cortex and movement. I. Movement selection and reaching. Exp. Brain Res. *117*, 292–310.
43. Snyder, L.H. (2000). Coordinate transformations for eye and arm movements in the brain. Curr. Opin. Neurobiol. *10*, 747–754.
44. Macaluso, E., Frith, C.D., and Driver, J. (2002). Supramodal effects of covert spatial orienting triggered by visual or tactile events. J. Cogn. Neurosci. *14*, 389–401.
45. Henson, R.N.A., Buechel, C., Josephs, O., and Friston, K. (1999). The slice-timing problem in event-related fMRI. Neuroimage *9*, 125.
46. Collins, D.L., Neelin, P., Peters, T.M., and Evans, A.C. (1994). Automatic 3D intersubject registration of MR volumetric data in standardized Talairach space. J. Comput. Assist. Tomogr. *18*, 192–205.
47. Holmes, A.P., and Friston, K.J. (1998). Generalisability, random effects and population inference. Neuroimage *7*, 754.
48. Price, C.J., and Friston, K.J. (1997). Cognitive conjunction: a new approach to brain activation experiments. Neuroimage *5*, 261–270.
49. Friston, K.J., Holmes, A.P., Price, C.J., Buchel, C., and Worsley, K.J. (1999). Multisubject fMRI studies and conjunction analyses. Neuroimage *10*, 385–396.
50. Worsley, K.J., Marrett, S., Neelin, P., Vandal, A.C., Friston, K.J., and Evans, A.C. (1996). A unified statistical approach for determining significant signals in images of cerebral activation. Hum. Brain Map. *4*, 58–73.